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Development and Validation of a Laser Diffraction-Based Particle Size Characterization Method for Carbamazepine Oral Suspension USP (100 mg/5 mL)

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ABSTRACT
Particle size distribution (PSD) is a critical quality attribute in pharmaceutical suspensions, as it directly influences physical stability, sedimentation behavior, redispersibility, dissolution rate, dose uniformity, and bioavailability. Carbamazepine Oral Suspension USP (100 mg/5 mL), a widely used anticonvulsant formulation, contains a poorly water-soluble active pharmaceutical ingredient whose therapeutic performance can be significantly affected by particle size characteristics. The present study was undertaken to develop and validate a reliable analytical method for determining the particle size distribution of Carbamazepine Oral Suspension USP (100 mg/5 mL) using laser diffraction technology. Particle size measurements were performed using a Malvern Mastersizer 3000 equipped with a Hydro 3000 (S) wet dispersion unit. Sample preparation and analytical conditions were optimized to ensure uniform dispersion and accurate particle size characterization. The developed method was validated in accordance with established analytical validation principles with respect to precision, intermediate precision, and robustness. Method precision was evaluated through six independent sample preparations, while intermediate precision was assessed by a second analyst on a different day. Robustness was examined by introducing deliberate variations in critical analytical parameters. The obtained results demonstrated acceptable variability, with percentage relative standard deviation (%RSD) values remaining within predefined acceptance criteria for d(0.1), d(0.5), and d(0.9) particle size measurements. The validation data confirmed that the developed method is precise, reproducible, and robust for the assessment of particle size distribution in Carbamazepine Oral Suspension USP (100 mg/5 mL). The method is suitable for routine quality control testing, formulation development, process monitoring, and stability studies. Consequently, the validated procedure provides a reliable analytical tool for ensuring consistent product quality, performance, and regulatory compliance throughout the product lifecycle.

Keywords: Carbamazepine Oral Suspension, Particle Size Distribution (PSD), Laser Diffraction, Method Validation, Malvern Mastersizer 3000

INTRODUCTION

Carbamazepine Oral Suspension (100 mg/5 mL) is an important liquid dosage form widely prescribed for the treatment of epilepsy, trigeminal neuralgia, and bipolar affective disorders, especially in pediatric and geriatric populations where administration of solid oral dosage forms may be challenging[1]. Carbamazepine is a dibenzazepine derivative that exhibits anticonvulsant and mood-stabilizing properties by reducing excessive neuronal excitability. Its pharmacological activity is primarily attributed to the inhibition of voltage-gated sodium channels, which suppresses repetitive neuronal discharge and stabilizes nerve cell membranes [2-3].Carbamazepine possesses a molecular formula of $C_{15}H_{12}N_2O$ and a molecular weight of 236.27 g/mol [4]. It occurs as a white to slightly off-white crystalline powder and is chemically identified as 5H-dibenz[b,f]azepine-5-carboxamide [5]. The drug demonstrates limited aqueous solubility while exhibiting good membrane permeability, placing it within the Biopharmaceutics Classification System (BCS) Class II category [6]. Owing to its poor water solubility, the rate and extent of dissolution are strongly influenced by particle size, which in turn can affect the drug's bioavailability and therapeutic performance [7]. For suspension dosage forms, particle size distribution is a critical physicochemical characteristic that significantly influences product quality. The size and distribution of suspended drug particles can affect sedimentation rate, ease of redispersion, dissolution behavior, dose uniformity, physical stability, and overall patient acceptability [8]. Inconsistent particle size may result in variable drug release and non-uniform dosing, potentially compromising product efficacy and safety. Therefore, establishing an appropriate particle size distribution profile is essential for maintaining the quality and performance of Carbamazepine Oral Suspension throughout its intended shelf life. Although numerous analytical methods such as high-performance liquid chromatography, ultra-performance liquid chromatography, gas chromatography, UV-visible spectrophotometry, and other instrumental techniques have been extensively employed for the quantitative estimation of carbamazepine, comparatively few studies have focused on the development and validation of particle size distribution methods for Carbamazepine Oral Suspension (100 mg/5 mL) [9-12]. In view of the importance of particle size as a critical quality attribute, the present investigation was designed to develop and validate a reliable particle size distribution method using a Malvern Mastersizer 3000 operating in wet dispersion mode. The method was

systematically evaluated and validated to ensure its accuracy, precision, reproducibility, and suitability for routine pharmaceutical quality control applications. The authors express their appreciation to Dr. Nataraj Palaniyappan, Novitium Pharma LLC, USA, for his noteworthy contributions to the field of particle size characterization in pharmaceutical sciences. His previously published work entitled Analytical Method Development and Validation to Assess the Particle Size Distribution in Azithromycin Oral Suspension 200 mg/5 mL provided valuable scientific insight and served as an important reference during the conceptualization of the present study [13]. The technical knowledge, methodological framework, and scientific perspectives derived from his research contributed significantly to the successful execution and overall quality of this investigation[14-15].

MATERIALS AND METHODS

Materials

Carbamazepine oral suspension (100 mg/5 mL)

Instrumentation and Equipment

A Malvern Mastersizer 3000 particle size analysis system equipped with both Aero S (dry dispersion) and Hydro MV (wet dispersion) accessories was employed for particle size measurements. Data acquisition, processing, and analysis were carried out using Mastersizer software with version of 3.88.

Instrumental Parameters

Particle size distribution analysis was performed using a Malvern Mastersizer 3000 equipped with a Hydro MVwet dispersion unit. Carbamazepine Oral Suspension USP (100 mg/5 mL) was used as the test sample. The refractive index of the sample was set at 1.669, while water was employed as the dispersant with a refractive index of 1.33. An absorption value of 0.1 was applied during the analysis. Measurements were conducted using the general-purpose analysis model with normal sensitivity settings, assuming an irregular particle shape. The measurement time and background measurement time were each maintained at 10 seconds. Obscuration levels were controlled within the range of 5%–15% to ensure optimal particle detection and data quality. The stirrer speed was maintained at 2000 rpm throughout the analysis, and three measurement cycles were performed for each sample. Ultrasonic dispersion was not utilized during the study. A pre-measurement delay of 30 seconds was applied prior to data acquisition to allow stabilization of the sample dispersion system. These conditions were optimized to obtain accurate, precise, and reproducible particle size distribution measurements for Carbamazepine Oral Suspension USP (100 mg/5 mL).

Sample Preparation

Sample Preparation and Particle Size Distribution Analysis

Prior to analysis, the Carbamazepine Oral Suspension (100 mg/5 mL) sample was shaken thoroughly for approximately 30 seconds to ensure uniform dispersion of the suspended particles. An aliquot of 5 mL of the suspension was transferred into a 30 mL stoppered test tube, followed by the addition of 15 mL of purified water. The mixture was vortexed for 1 minute to achieve adequate dispersion and subsequently sonicated for 5 minutes to break down any agglomerates and obtain a homogeneous suspension. The prepared sample was then added dropwise into the sampling unit, and the system was allowed to equilibrate for 5–10 minutes until a stable obscuration level was achieved. The sampling unit of the Malvern Mastersizer 3000 was filled to the brim with dispersant solution, and the accessory settings were configured through the instrument software. The stirrer/pump speed was gradually increased to 2000 rpm to ensure uniform circulation and dispersion of particles within the measurement cell. Any displaced dispersant was replenished to maintain the liquid level. Instrument parameters were verified according to the approved standard operating procedure (SOP) for wet particle size analysis. Prior to sample measurement, the system was degassed two to three times to eliminate air bubbles that could interfere with the laser diffraction measurements. A background measurement was then performed using the predefined SOP. If the laser intensity of the background measurement was found to be below 50%, the sampling unit was drained, cleaned, and the background measurement was repeated until acceptable conditions were achieved. Following successful background verification, sample identification details were entered into the software. The prepared sample was introduced into the sampling unit dropwise while continuously monitoring the obscuration level. The suspension was allowed to stabilize for approximately 5–10 minutes until the obscuration remained constant within the target range of 5–15%. Particle size distribution measurements were subsequently performed, and the average results generated by the instrument software were recorded and printed for further evaluation. This procedure ensured accurate, reproducible, and reliable characterization of the particle size distribution of Carbamazepine Oral Suspension (100 mg/5 mL).

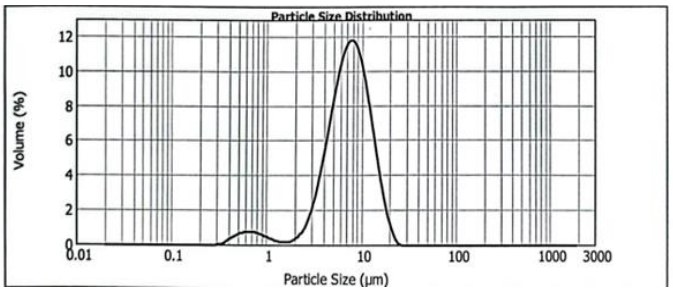

Fig.1

RESULTS AND DISCUSSION

Method Validation

Method Precision

The precision of the particle size approach has been assessed by placing six various sample preparations into the sampling instrument and documenting the particle size distribution. %RSDs for particle sizes at d (0.1),d (0.5), and d(0.9) should not exceed 15% and 10%, respectively. (**Table 1)**

Table 1: Results for Precision study

Run No.	d(0.1)	d(0.5)	d(0.9)
1	2.455	10.542	18.352
2	2.156	10.854	18.543
3	2.254	10.239	18.853
4	2.578	10.745	18.965
5	2.456	10.963	18.782
6	2.568	10.826	18.396
Average	2.41	10.69	18.65
%RSD	7.1	2.5	1.4

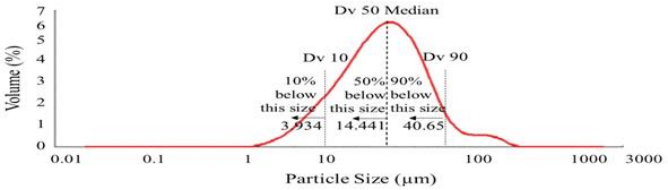

Fig.2

Robustness

By varying instrument parameters like sonication rate±10% and obscuration by ±10%. One can evaluate the process's resilience. Following the determination of the particle size distribution (PSD) of the sample, the percentage relative standard deviation (%RSD) values for d(0.1), d(0.5), and d(0.9) were calculated. The acceptance criteria required the %RSD values at d(0.1) and d(0.9) to be not more than 15%, while the %RSD at d(0.5) was required to be not more than 10% Tables 2 and 3.

Table 2: Results for Robustness–(Agitation Rate)

Run No.	Agitation Rate	d(0.1)	d(0.5)	d(0.9)
1	**+10%**	2.356	10.526	19.652
2		2.248	10.745	18.958
3		2.657	10.685	18.658
Average		2.42	10.65	19.09
%RSD		8.8	1.1	2.7
1	-10%	2.122	10.352	18.365
2		2.254	10.459	18.749
3		2.422	10.965	18.618
Average		2.27	10.59	18.58
%RSD		6.6	3.1	1.1

Table 3: Results for Robustness –(Obscuration)

Run No.	Obscuration	d(0.1)	d(0.5)	d(0.9)
1	**+10%**	2.225	10.436	18.635
2		2.296	10.238	18.726
3		2.356	10.853	18.653
Average		2.29	10.51	18.67
%RSD		2.9	3.0	0.3
1	**-10%**	2.352	10.746	18.963
2		2.357	10.635	18.857
3		2.391	10.527	18.376
Average		2.37	10.64	18.73
%RSD		0.9	1.0	1.7

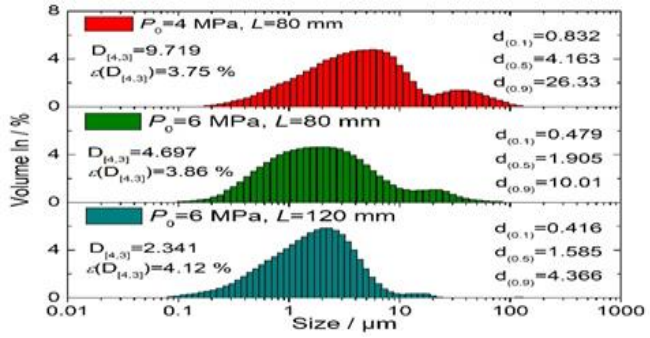

Fig.3

Intermediate precision

Analyst-2 documented the particle size distribution after moving six distinct sample preparations into the sampling apparatus on a separate day. to evaluate the reliability of the particle size approach. Particle size percentage RSD at d(0.1), d(0.9), and d(0.5) should not be greater than 15% for (0.1), d(0.9), and d(0.5), and 10% for d(0.5**)** (Table 4)

Table 4: Observed values for Intermediate Precision

Run No.	Analyst-1			Analyst-2		
	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)
1	2.455	10.542	18.352	2.635	10.856	18.674
2	2.156	10.854	18.543	2.453	10.478	18.958
3	2.254	10.239	18.853	2.396	10.965	18.517
4	2.578	10.745	18.965	2.567	10.365	18.248
5	2.456	10.963	18.782	2.451	10.685	18.357
6	2.568	10.826	18.396	2.572	10.485	18.652
Average	2.41	10.69	18.65	2.51	10.64	18.57
%RSD	7.1	2.5	1.4	3.7	2.2	1.4

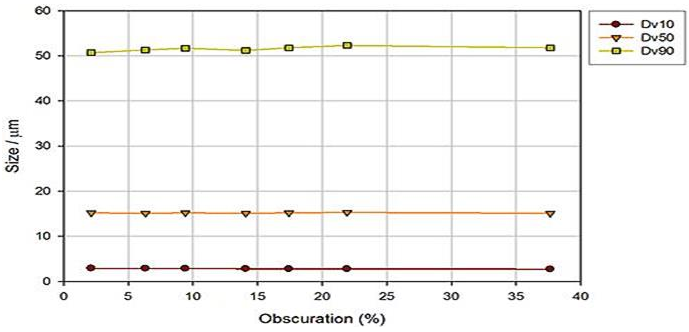

Fig.4

DISCUSSION

The present investigation successfully established and validated a scientifically robust particle size distribution (PSD) method for Carbamazepine Oral Suspension USP (100 mg/5 mL) using laser diffraction technology. Particle size characterization is recognized as a critical quality attribute (CQA) for oral suspension formulations because it significantly influences the physical stability, sedimentation rate, redispersibility, dissolution behavior, dose uniformity, bioavailability, and therapeutic efficacy of the final pharmaceutical product. In suspension dosage forms, inappropriate particle size distribution may result in particle aggregation, non-uniform dosing, caking during storage, and inconsistent product performance. Therefore, development of a reliable, reproducible, and regulatory-compliant PSD analytical method is essential for both product development and routine quality control applications.

Laser diffraction technology was selected for the present study because of its rapid analysis capability, broad dynamic size range, high reproducibility, and suitability for wet dispersion systems commonly used in pharmaceutical suspensions. Compared with traditional microscopic techniques, laser diffraction offers superior statistical representation of particle populations and minimizes operator-dependent variability. The use of the Malvern Mastersizer 3000 enabled accurate determination of cumulative particle size parameters including d(0.1), d(0.5), and d(0.9), which collectively provide comprehensive information regarding the particle size distribution profile of the formulation. Method precision was evaluated by analyzing six independently prepared sample dispersions under optimized analytical conditions. The obtained mean particle size values for d(0.1), d(0.5), and d(0.9) were 2.41

µm, 10.69 µm, and 18.65 µm, respectively. The corresponding %RSD values of 7.1%, 2.5%, and 1.4% demonstrated excellent repeatability of the developed method. The relatively low variability observed across replicate preparations indicates that the sample preparation procedure, dispersion conditions, and instrumental settings were adequately controlled and capable of producing consistent PSD measurements. The results also confirmed that the analytical method was sufficiently sensitive to characterize the suspension system without introducing significant experimental variability.

Robustness studies were performed to evaluate the influence of deliberate variations in critical analytical parameters, specifically agitation rate and obscuration level, on the measured particle size distribution. Agitation plays a vital role in maintaining homogeneous suspension dispersion during measurement, while obscuration directly affects laser signal intensity and particle detection efficiency. The robustness assessment demonstrated that small variations of ±10% in agitation rate and obscuration did not significantly alter the PSD results. The %RSD values obtained for d(0.1), d(0.5), and d(0.9) under all modified conditions remained within the predefined acceptance limits, thereby confirming the reliability and ruggedness of the method. These findings indicate that the developed procedure possesses sufficient operational flexibility and is unlikely to be adversely affected by normal laboratory variations encountered during routine analysis.

Intermediate precision was evaluated to determine the reproducibility of the method under inter-analyst and inter-day conditions. A second analyst performed the analysis on a different day using freshly prepared sample dispersions. The particle size values generated by Analyst-2 showed excellent agreement with those obtained by Analyst-1, with all %RSD values remaining well within acceptance criteria. The close similarity between the two datasets confirmed that the method is highly reproducible and not significantly influenced by analyst-dependent operational differences or day-to-day instrumental variability. Such reproducibility is particularly important for analytical methods intended for routine quality control environments where multiple analysts may perform testing over extended product lifecycle periods.

The optimized analytical conditions established during method development contributed significantly to the overall reliability of the PSD measurements. Water was selected as the dispersing medium due to its compatibility with the formulation matrix and its ability to maintain stable particle dispersion without inducing particle dissolution or aggregation. Controlled obscuration levels between 5% and 15% ensured optimal laser transmission and minimized multiple scattering effects during measurement. In addition, optimized stirring conditions effectively prevented particle sedimentation and maintained uniform sample dispersion throughout the analytical run. Collectively, these parameters enabled accurate and reproducible characterization of the particle size distribution profile of Carbamazepine Oral Suspension USP (100 mg/5 mL).

The validated method demonstrated strong analytical performance characteristics and fulfilled all predefined validation acceptance criteria. The low variability observed throughout precision, robustness, and intermediate precision studies confirms that the developed laser diffraction method is suitable for its intended analytical purpose. The method can therefore be reliably implemented for routine quality control testing, formulation development studies, process optimization, manufacturing scale-up activities, comparative product evaluation, and long-term stability monitoring of carbamazepine suspension formulations.

Furthermore, the present study highlights the applicability of laser diffraction technology as an efficient analytical approach for characterization of oral suspension products in the pharmaceutical industry. Accurate PSD determination is essential not only for ensuring consistent product quality but also for supporting regulatory compliance and maintaining batch-to-batch consistency throughout commercial manufacturing. The validated method thus provides a valuable analytical tool for comprehensive particle size characterization of Carbamazepine Oral Suspension USP (100 mg/5 mL).

CONCLUSION

A scientifically sound, robust, accurate, and reproducible particle size distribution (PSD) method was successfully developed and validated for Carbamazepine Oral Suspension USP (100 mg/5 mL) using a Malvern Mastersizer 3000 operating in wet dispersion mode. The optimized analytical conditions, including appropriate dispersing medium selection, controlled obscuration range, and optimized agitation settings, enabled effective sample dispersion and accurate determination of particle size parameters including d(0.1), d(0.5), and d(0.9).

Comprehensive method validation studies demonstrated that the developed analytical procedure exhibited excellent precision, intermediate precision, and robustness. The low %RSD values obtained during repeatability and reproducibility studies confirmed the consistency and reliability of the method for routine analytical application. In addition, deliberate variations in critical operating parameters such as agitation rate and obscuration level did not significantly influence the measured particle size distribution, thereby establishing the ruggedness and operational robustness of the procedure.

The developed laser diffraction method was found to be highly suitable for accurate characterization of the particle size distribution profile of Carbamazepine Oral Suspension USP (100 mg/5 mL). The validated method can be effectively utilized for routine quality control analysis, formulation development, process optimization, manufacturing support, comparative product evaluation, and stability assessment studies. Moreover, the method provides a reliable analytical platform for ensuring batch-to-batch consistency, maintaining product quality attributes, and supporting regulatory compliance throughout the pharmaceutical product lifecycle.

Overall, the present study demonstrates that laser diffraction technology represents a rapid, reliable, and efficient analytical approach for PSD characterization of pharmaceutical suspension dosage forms. The validated method offers significant practical applicability in pharmaceutical analytical laboratories and

serves as an important quality assessment tool for ensuring the safety, efficacy, and performance of carbamazepine oral suspension products.

CONFLICT OF INTERESTS
The authors declare no conflict of interest

ETHICS APPROVAL
Not applicable

FUNDING
This study received no specific funding from public, commercial, or not for profit funding agencies.

AI TOOL DECLARATION
The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY
Data will be available on request

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